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10/14/04 Michelle Hobson
Date Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

BARNETT et al.

Serial No.: 09/610,313

Filing Date: July 5, 2000

Title: POLYNUCLEOTIDES ENCODING ANTIGENIC HIV TYPE C POLYPEPTIDE, POLYPEPTIDES AND USES THEREOF

Examiner: B. Whiteman

Group Art Unit: 1635

Confirmation No.: 4221

AMENDMENT AFTER FINAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Sir:

This amendment is filed in response to the Office Action, mailed on June 14, 2004. Applicants request a one-month extension of time and attach the appropriate fee, making a response due on or before October 14, 2004. Therefore, this response is timely filed.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims begin on page 3 of this paper.

Remarks begin on page 8 of this paper.

AMENDMENTS TO THE SPECIFICATION

Please amend the paragraph beginning on page 1, line 6 as follows:

This application is a continuation-in-part of U.S. Serial No. 09/475,704, filed December 30, 1999 (pending), which in turn is related to provisional patent applications serial nos. 60/114,495, filed December 30, 1998 and 60/162,195, filed September 30, 1999, from which priority is claimed under35 U.S.C. § 119(e)(1) and which applications are incorporated herein by reference in their entireties.

On pages 74-75, please replace the paragraph bridging pages 74 and 75 with the following:

To construct a DHFR cassette, the EMCV IRES (internal ribosome entry site) leader was PCR-amplified from pCite-4a+ (Novagen, Inc., Milwaukee, WI) and inserted into pET-23d (Novagen, Inc., Milwaukee, WI) as an Xba-Nco fragment to give pET-EMCV. The dhfr gene was PCR-amplified from pESN2dhfr to give a product with a Gly-Gly-Gly-Ser (SEQ ID NO: 46) spacer in place of the translation stop codon and inserted as an Nco-BamH1 fragment to give pET-E-DHFR. Next, the attenuated neo gene was PCR amplified from a pSV2Neo (Clontech, Palo Alto, CA) derivative and inserted into the unique BamH1 site of pET-E-DHFR to give pET-E-DHFR/Neo(m2). Finally the bovine growth hormone terminator from pCDNA3 (Invitrogen, Inc., Carlsbad, CA) was inserted downstream of the neo gene to give pET-E-DHFR/Neo(m2)BGHt. The EMCV-dhfr/neo selectable marker cassette fragment was prepared by cleavage of pET-E-DHFR/Neo(m2)BGHt.

AMENDMENTS TO THE CLAIMS

This listing of the claims replaces all prior listings and versions:

1. (currently amended): An expression cassette, comprising

a polynucleotide sequence operably linked to a promoter, wherein the polynucleotide sequence encodes an HIV ~~*Pol*~~ polypeptide that elicits a *Pol*-specific immune response, and further wherein the polynucleotide sequence encoding said ~~*Pol*~~ polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented of Figure 8 (SEQ ID NO:30); Figure 9 (SEQ ID NO:31); or Figure 10 (SEQ ID NO:32).

2. (original): The expression cassette of claim 1, further comprising one or more nucleic acids encoding one or more viral polypeptides or antigens.

3. (original): The expression cassette of claim 2, wherein the viral polypeptide or antigen is selected from the group consisting of Gag, Env, vif, vpr, tat, rev, vpu, nef and combinations thereof.

4. (previously presented): The expression cassette of claim 1, further comprising one or more nucleic acids encoding one or more cytokines.

5. (previously presented): A recombinant expression system for use in a selected host cell, comprising, the expression cassette of claim 1, and wherein said polynucleotide sequence is operably linked to control elements compatible with expression in the selected host cell.

6. (original): The recombinant expression system of claim 5, wherein said control elements are selected from the group consisting of a transcription promoter, a transcription enhancer element, a transcription termination signal, polyadenylation sequences, sequences for optimization of initiation of translation, and translation termination sequences.

7. (original): The recombinant expression system of claim 5, wherein said transcription promoter is selected from the group consisting of CMV, CMV+intron A, SV40, RSV, HIV-Ltr, MMLV-ltr, and metallothionein.

8. (previously presented): A cell comprising the expression cassette of claim 1, and wherein said polynucleotide sequence is operably linked to control elements compatible with expression in the selected cell.

9. (original): The cell of claim 8, wherein the cell is a mammalian cell.

10. (original): The cell of claim 9, wherein the cell is selected from the group consisting of BHK, VERO, HT1080, 293, RD, COS-7, and CHO cells.

11. (original): The cell of claim 10, wherein said cell is a CHO cell.

12. (original): The cell of claim 8, wherein the cell is an insect cell.

13. (original): The cell of claim 12, wherein the cell is either *Trichoplusia ni* (Tn5) or Sf9 insect cells.

14. (original): The cell of claim 8, wherein the cell is a bacterial cell.

15. (original): The cell of claim 8, wherein the cell is a yeast cell.

16. (original): The cell of claim 8, wherein the cell is a plant cell.

17. (original): The cell of claim 8, wherein the cell is an antigen presenting cell.

18. (original): The cell of claim 17, wherein the antigen presenting cell is a lymphoid cell selected from the group consisting of macrophage, monocytes, dendritic cells, B-cells, T-cells, stem cells, and progenitor cells thereof.

19. (original): The cell of claim 8, wherein the cell is a primary cell.

20. (original): The cell of claim 8, wherein the cell is an immortalized cell.

21. (previously presented): The cell of claim 8, wherein the cell is a tumor cell.

22. (previously presented): A composition for generating an immunological response, comprising the expression cassette of claim 1.

23. (original): The composition of claim 22, further comprising one or more *Pol* polypeptides.

24. (original): The composition of claim 23, further comprising an adjuvant.

25. (previously presented): A composition for generating an immunological response, comprising the expression cassette of claim 2.

26. (original): The composition of claim 25, further comprising a *Pol* polypeptide.

27. (original): The composition of claim 26, further comprising one or more polypeptides encoded by the nucleic acid molecules of claim 2.

28. (original): The composition of claim 27, further comprising an adjuvant.

29. (previously presented): A method of generating an immune response in a subject, comprising,

introducing the composition of claim 22 into said subject under conditions that are compatible with expression of said expression cassette in said subject.

30. (original): The method of claim 29, wherein said expression cassette is introduced using a gene delivery vector.

31. (original): The method of claim 30, wherein the gene delivery vector is a non-viral vector.

32. (original): The method of claim 30, wherein said gene delivery vector is a viral vector.

33. (original): The method of claim 32, wherein said gene delivery vector is a Sindbis-virus derived vector.

34. (original): The method of claim 32, wherein said gene delivery vector is a retroviral vector.

35. (original): The method of claim 32, wherein said gene delivery vector is a lentiviral vector.

36. (previously presented): The method of claim 30, wherein said composition is delivered by using a particulate carrier.

37. (original): The method of claim 30, wherein said composition is coated on a gold or tungsten particle and said coated particle is delivered to said subject using a gene gun.

38. (original): The method of claim 30, wherein said composition is encapsulated in a liposome preparation.

39. (original): The method of any of claims 30-38, wherein said subject is a mammal.

40. (original): The method of claim 39, wherein said mammal is a human.

41 to 42. (canceled).

43. (previously presented): The method of claim 42, where the method further comprises administration of a polypeptide derived from an HIV.

44. (original): The method of claim 43, wherein administration of the polypeptide to the subject is carried out before introducing said expression cassette.

45. (original): The method of claim 43, wherein administration of the polypeptide to the subject is carried out concurrently with introducing said expression cassette.

46. (original): The method of claim 43, wherein administration of the polypeptide to the subject is carried out after introducing said expression cassette.

47. (original): The expression cassette of claim 2, wherein the viral polypeptide or antigen is selected from the group consisting of polypeptides derived from hepatitis B, hepatitis C and combinations thereof.

48. (original): An expression cassette comprising the polynucleotide sequence of SEQ ID NO:30, SEQ ID NO:31 or SEQ ID NO:32.

49. (previously presented): The expression cassette of claim 48 further comprising a nucleotide sequence encoding a viral polypeptide selected from the group consisting of Gag, Env, vif, vpr, tat, rev, vpu, nef, and combinations thereof.

50. (original): A composition for generating an immunological response in a mammal comprising the expression cassette of claim 48.

51. (original): A method of generating an immune response in a mammal, the method comprising the step of intramuscularly administering the expression cassette of claim 48 to said mammal.

REMARKS

STATUS OF THE CLAIMS

Claims 1-40 and 43-51 were pending. As shown above, claim 1 has been amended to indicate that the claimed polynucleotides encode an HIV polypeptide, which polypeptide elicits a *Pol*-specific immune response. As noted by the Examiner, the specification teaches that sequences encoding polypeptides that do not exhibit non-immunogenic "*Pol*" functions (*e.g.*, reverse transcriptase activity) are included within the scope of the claims, so long as the polypeptides elicit a *Pol*-specific immune response. *See, e.g.*, page 73 of the specification. The amendments are made to expedite prosecution and are not made for reasons related to patentability. Thus, claims 1-40 and 43-51 are pending as shown above.

SPECIFICATION

Applicants have amended the specification to indicate that the non-provisional parent application remains pending, as requested by the Examiner on page 2 of the Final Office Action.

In addition, Applicants have inserted the appropriate sequence identifier on page 75 of the specification. A new Sequence Listing is also submitted herewith.

FUNCTIONAL LANGUAGE

In the Final Office Action, it was maintained that the claims still read on polypeptides having the functional characteristics of a wild-type HIV *Pol* polypeptide. *See, e.g.*, page 13 of the Final Office Action.

The foregoing amendments obviate this concern, inasmuch as the claims do not read on sequences that necessarily encode a "*Pol*" polypeptide, but rather, encompass sequences that encode any polypeptide that elicits a *Pol*-specific immune response. In other words, the claims no longer read on sequences encoding a *Pol* polypeptide, with all the various functions intrinsic to *Pol* polypeptides. Thus, as discussed during the telephone interview held on October 5, 2004, the foregoing amendments render moot the Examiner's primary concerns about the functions of the polypeptides encoded by the claimed sequences.

INTERVIEW

Applicants thank Examiner Whiteman for taking the time to talk with the undersigned and Dr. Michael Moran by telephone on Tuesday, October 5, 2004 regarding the remaining issues under 35 U.S.C. § 112, first paragraph (enablement and description). Applicants address the issues set forth in the Final Office Action, and discussed by telephone, below.

35 U.S.C. § 112, FIRST PARAGRAPH, ENABLEMENT AND DESCRIPTION

A. INOPERATIVE EMBODIMENTS

During the telephone conference, the Examiner reiterated that there may be polynucleotide sequences falling within the 90% identity requirement that do not encode an immunogenic polypeptide and, accordingly, that it would require undue experimentation to determine operative species, other than those disclosed in the specification.

Applicants reiterate that the presence of inoperative embodiments does not necessarily render a claim nonenabled. *See, e.g.,* MPEP § 2164.08(b); and *In re Angstadt,* 537 F.2d 498, 504, 190 USPQ 214, 219, CCPA 1976. The test of enablement is not what is predictable *a priori*, but what the specification teaches the skilled practitioner in regard to the claimed subject matter. Thus, not every species (or even a majority of species) encompassed by the claims, even in an unpredictable area like the chemical sciences, needs to be disclosed. *In re Angstadt,* 537 F.2d 498, 504, 190 USPQ 214, 219, CCPA 1976. The notion that one of ordinary skill in the art must have reasonable assurances of obtaining positive results on every occasion has been emphatically rejected. *Angstadt* at 219. So long as it is clear that some species render the claims operative, the inclusion of possible inoperative species cannot invalidate the claim under paragraph 1 of 35 U.S.C. §112. *See, also, In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, CCPA 1971; *Horton v. Stevens*, 7 USPQ2d 1245, 1247, Fed. Cir. 1988.

In the pending case, Applicants again note that every single nucleotide species exhibiting 90% identity to SEQ ID NOs: 30, 31 or 32 can be determined *a priori* and, as such, the entire genus of polynucleotides exhibiting 90% identity to these sequences is enabled by the specification as filed.[1] Likewise, the polypeptide encoded by each and every one of these sequences can also be determined *a priori*. Thus, there are no inoperative "structural" embodiments encompassed by the claims and, as such, the specification clearly enables the structures (sequences) of the claims.

Moreover, as set forth in the case law described above, the possibility that there may be some inoperative "functional" embodiments (*e.g.,* some of the polypeptides may not elicit a *Pol*-specific immune response) does not render the specification nonenabling because the specification clearly teaches how to test for immunogenicity and indicates that such testing is utterly routine. *See, e.g.,* Declarations of Record. Routine experimentation, as would be

[1] Applicants also direct the Examiner's attention to Example N:DNA of the Patent Office's "Training Materials for Examining Patent Applications with respect to 35 U.S.C. § 112, First Paragraph -- Enablement -- Chemical/Biotechnical Applications," which states that even with a very large genus of sequences (at least 1.26×10^{21}), undue experimentation is not required to determine all members of the genus because "each embodiment can be readily identified using the genetic code, synthesized using conventional methods, and used in the manner taught in the specification." see, page N-4.

required to determine if an embodiment falls within the "functional" scope of the claims, is not undue experimentation.[2]

Thus, not only does the claim language itself exclude inoperative embodiments, namely any and all nucleotide sequences that encode polypeptides that do not elicit *Pol*-specific immune responses, the experimentation needed to identify inoperative embodiments is not undue. Accordingly, the presence of potentially inoperative functional embodiments cannot form grounds for rejecting the pending claims as allegedly nonenabled.

B. STRUCTURE:FUNCTION CORRELATION

During the telephone conference, Examiner Whiteman also indicated that the specification is not enabling because it does not set adequately set forth a correlation between the structure of the polypeptide encoded by the claimed sequences and the functions of these polypeptides, for example by not enumerating "essential" nucleotides that are required in order to encode an immunogenic polypeptide.

As Applicants noted during the telephone conference, the correlation between polypeptide structure (primary sequence or tertiary structure) and immunogenic function can tolerate many modifications. In other words, whereas essential residues are readily identifiable for enzymatic (*e.g.*, catalytic) functions, any polypeptide can tolerate multiple substitutions at various residues while still retaining its immunogenic function.[3]

Furthermore, as noted above, the claims no longer encompass sequences encoding a polypeptide having enzymatic or catalytic functions of a *Pol* polypeptide. Thus, this concern is obviated by the foregoing amendments.

C. THE SPECIFICATION DESCRIBES CLAIMED IMMUNOGENIC FUNCTION

Written description, particularly as it relates to the recited immunogenic function, was also discussed during the telephone conference. In this regard, Examiner Whiteman invited Applicants to present a copy of relevant PowerPoint slides presented by Christopher Low at the BioScience Forum on Thursday, September 9, 2004. (Appendix A, attached hereto).

In this presentation, Examiner Low indicated that a claim essentially identical to independent claim 1 as presented herein satisfied the written description requirement because the specification set forth "sufficient support" that the protein encoded by the claimed genus of

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[2] *See, also, United States v. Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied,* 490 U.S. 1046 (1989)), holding that routine experimentation, even if extensive (on the order of six or more months and tens of thousands of dollars), is not necessarily undue.

[3] Nor does immunogenic function necessarily depend on tertiary structure. Simply put, wild type folding is not critical to generating an immune response and, accordingly, the references cited on page 14 of the Final Office Action are not relevant to the enablement or description inquiry.

polynucleotides had a specific, substantial, and credible use related to the claimed activity ("activity X"). *See, e.g.,* slide #17 of Examiner's Low presentation, where the exemplary claim reads:

> An isolated and purified nucleic acid comprising a nucleotide sequence that is 90% identical to SEQ ID NO:1, wherein said nucleic acid encodes a protein having activity X.

Indeed, the exemplary claim presented in Examiner Low's presentation is the polynucleotide equivalent of the claim presented in Example 14 of the PTO's "Synopsis of Application of Written Description Guidelines." Both of these exemplary claims are considered adequately described in view of a specification that discloses examples of sequences having the claimed activity and methods of determining the presence or absence of such activity.[4]

Thus, like Examiner Low's example and like Example 14, the specification as filed provides sufficient support demonstrating that the protein has a specific, substantial and credible use related to immunogenicity. Thus, the written description requirement is satisfied.

D. FURTHER EVIDENCE OF ENABLEMENT AND ADEQUATE DESCRIPTION

Applicants also submit herewith further evidence establishing the patentability of the claims as pending. In particular, Applicants direct the Examiner's attention to U.S. Patent No. 6,602,705, an issued patent with claims and disclosure highly analogous to those in the pending case, the difference being that U.S. Patent No. 6,602,705 claims polynucleotide sequences derived from subtype B sequences while the pending application claims sequences derived from subtype C sequences. Indeed, the guidance provided by this issued Patent regarding percent homology and assaying immunogenicity is virtually identical to that provided in the pending specification. Thus, U.S. Patent No. 6,602,705, an issued and presumptively valid U.S. Patent, provides still further evidence that the Patent Office considers claims such as those pending herein to be adequately described and fully enabled.

PROVISIONAL OBVIOUSNESS-TYPE DOUBLE PATENTING

Applicants request the provisional double patenting rejection be held in abeyance until indication as at allowable claims is received in one of the applications.

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[4] In addition, Applicants note again how their description of particular sequences and recitation of these sequences in the claims distinguishes the pending case from *University of California v. Eli Lilly*. In *Eli Lilly*, the claims failed to recite any reference sequence whatsoever and, therefore, the genus encompassed by the claims included any polynucleotide encoding insulin. In contrast, the genus encompassed by the pending claims is fully described because every sequence exhibiting 90% identity can be envisioned from the reference sequences.

CONCLUSION

In view of the foregoing amendments, Applicants submit that the claims are now in condition for allowance and request early notification to that effect.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §1.16, §1.17, and §1.21, which may be required by this paper, or to credit any overpayment, to Deposit Account No. 18-1648, referencing Atty. Docket No. 2302-1631.20.

Please direct all further written communications regarding this application to:

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Respectfully submitted,

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Reach Through Claims/Percent Homology

Christopher Low, Ph.D.

SPE Art Unit 1614

Abstract:

Patentability issues of reach through claims directed to candidate compounds that might be identified by using basic screening methods and their downstream uses based on homology to other proteins and polynucleotides or similarity to other chemicals.

Biography:

Christopher Low is a Supervisory Patent Examiner for Art Unit 1614 in Technology Center 1600 at the USPTO overseeing the examination of patent applications drawn to bioaffecting compositions and methods, specifically organic chemical pharmaceuticals. He joined the USPTO in 1998, and became a Supervisory Patent Examiner in 2000. Chris has a BS in Biology from the University of Hawaii, a MS in Microbiology from the University of Hawaii, and a PhD from Oregon State University.

What % homology is appropriate?

- Distinguish over prior art
- Technology based
  - Do alignments yield information that suggests an appropriate amount of variation?

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Written Description

- An isolated and purified nucleic acid comprising a nucleotide sequence that is 90% identical to SEQ ID NO: 1.
- An isolated and purified nucleic acid comprising a nucleotide sequence that is 90% identical to SEQ ID NO: 1, wherein said nucleic acid encodes a protein having activity X.
  - The specification provides sufficient support that isolated protein has a specific, substantial, and credible use related to activity X.

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Functional language

- Claim language should set forth a function for a claimed product that is *specific, substantial, and credible*